Isophthalonitrile

CAS # 626-17-5

HPV Test Plan

Syngenta Crop Protection, Inc.

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Summary

Syngenta Crop Protection, Inc (Syngenta) has agreed to participate in the United States Environmental Protection Agency's (EPA) voluntary High Production Volume (HPV) Chemical Program. The objective of EPA's HPV program is to provide basic hazard information for chemicals manufactured at high volumes in the United States. Syngenta hereby submits the test plan for isophthalonitrile (CAS# 626-17-5), which is used as an intermediate in the production of certain agricultural chemicals (e.g., fungicides).

IUPAC Name: Isophthalonitrile

Common Name: 1,3-dicarbonitrile benzene

Abbreviation: IPN

CAS#: 626-17-5

This document provides the test plan for isophthalonitrile (CAS# 626-17-5) under the High Production Volume (HPV) Chemical Challenge Program. The test plan identifies existing data of adequate quality for isophthalonitrile, and outlines any the intended testing to be conducted.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, Syngenta has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data according to guidance provided by the HPV program. The reliability of the studies were assessed based on the standards/guidances specified by the USEPA (Klimisch et al, 1997; US EPA, 1999).

Based on the amount, type and quality of hazard assessment data available for isophthalonitrile, no additional studies are currently needed to fulfill the SIDS data set.

Data Review
In developing a rationale for isophthalonitrile's test plan, Syngenta utilized data from internal studies and data from available publications. If the quality of the reports and data were of sufficient quality based on Klimische, 1997, then a robust summary was prepared describing the report and the data quality.

Physical/Chemical Properties
Robust summaries were developed for melting point, boiling point, vapor pressure and water solubility. Secondary literature sources were used to derive values for boiling point and water solubility. Data is available for all endpoints. (See Table 1 and IUCLID document).

Conclusion
In summary, the current physical/chemical property database for isophthalonitrile meets the HPV data requirements. No additional testing is required nor needed.

Environmental Fate
No specific environmental fate studies exist for IPN. However, environmental fate modeling should provide sufficient understanding of its potential movement in soil, water and air.

Conclusion
Syngenta needs to conduct environmental fate modeling using the known physical/chemical properties of IPN. Syngenta will update this document when modeling results become available.

Ecotoxicology
The acute toxicity (96 hr LC_{50} values) in traditional toxicity testing species of fish was reported to be 110 mg/l (Oncorhynchus mykiss) and 170 mg/l (Lepomis macrochirus). (See Table 1 and IUCLID document). One journal article mentioned the LC50 of 20 – 40 for a another species of fish (Oryzias latipes). The EC50 of 44 mg/L for algae, although the quality of this information was not sufficient for inclusion.

Conclusion
Based on the acute toxicity characteristics of isophthalonitrile, it should be categorized as practically nontoxic to trout and bluegill; IPN is slightly toxic to Oryzias latipes. While there are no data for aquatic invertebrates, it is unlikely isophthalonitrile would be categorized as highly toxic to aquatic invertebrates. There are no data on the toxicity of isophthalonitrile to aquatic or terrestrial plants, however isophthalonitrile is not known to have significant weed control efficacy. It is unlikely isophthalonitrile will pose a risk to aquatic invertebrates or plants.

Mammalian Toxicology

Significant and adequate toxicity testing of isophthalonitrile for purposes of hazard assessment currently exists. Mouse and rat acute oral toxicity studies and repeat dose toxicity studies meet the quality criteria. In addition, there is a one-generation reproduction study in the rat that also meets the quality criteria. (See Table 1 and IUCLID document).

Acute Toxicity

The acute toxicity of isophthalonitrile has been adequately evaluated in rats and mice. The acute oral LD_{50} value in rats was found to be 1790 mg/kg in males and 860 mg/kg in females. The acute oral LD_{50} value in mice was determined to be 369 mg/kg. (See Table 1 and IUCLID document).

Repeat Dose Toxicity

A 90-day dietary rat toxicity study was conducted with isophthalonitrile. The NOAEL was determined to be 1 mg/kg/day based on the increased incidence of hyaline droplet formation and abnormal accumulation of alpha-2 μ-globulin in kidneys at 5 and 25 mg/kg/day. However, it has been previously established that this effect is not relevant to humans, and, therefore, the NOAEL for females was 5 mg/kg/ day. The NOAEL in a 90-day dietary mouse study was 20 mg/kg/day. The NOAEL in a 21-day dermal study in rabbits was 500 mg/kg/day. In a 14-day inhalation study, increased liver weight was seen in both sexes at 190 and 1250 mg/m^3 but was not associated with any histopathological changes. (See Table 1 and IUCLID document).

Genetic Toxicity

IPN was reported to be negative in an Ames bacterial mutagenicity assay and Chinese hamster lung chromosomal aberration test. (See Table 1 and IUCLID document).

Reproductive and Development Toxicity

No developmental toxicity test has been conducted with isophthalonitrile, however a combination 28-day toxicity and one-generation reproduction study was conducted in the rat. (See Table 1 and IUCLID document). Rats were dosed at 0, 5, 10, 25 and 50 mg/kg/day up to 122 days. NOEL levels were determined to be 5 and 25 mg/kg/day for the 28-day toxicity and reproduction endpoints, respectively. No evidence of obvious/gross teratogenicity was noted in the one generation reproduction study.

Conclusion

For the purposes of satisfying HPV toxicity testing requirements for hazard assessment, it is concluded that no additional mammalian toxicity testing is necessary or required.

References

Klimisch HJ, Andreae M and Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25:1-5.

US EPA, 1999. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

Table 1. Available data for Isophthalonitrile (CAS# 626-17-5)

Endpoint	IPN
Physical-Chemical Data	
Molecular weight	106.15
Physical state	solid
Melting Point	162 ºC
Boiling Point	275 ºC
Vapor Pressure	1.77 hPa at 100°C
Partition Coefficient (logPow)	0.39
Water Solubility	soluble
Environmental Fate	
Photodegradation	No data
Fugacity (distribution)	No data
Biodegradability	No data
Water Stability	No data
Ecotoxicology	
Acute Fish Toxicity 96 hrs LC50	110 mg/l 170 mg/l
Acute Invertebrate Toxicity 48 hrs LC50	No data
Algal Toxicity LC50	44 mg/L (unacceptable quality)
Mammalian Toxicology	
Acute Toxicity Oral Inhalation Dermal	 LD50 = 1790 mg/kg bw (male rats), 860 mg/kg bw (female rats) 369 mg/kg bw mouse LC50 > 8970 mg/m^3 (1 hr, rats) LD50 > 2000 mg/kg bw (dermal, rabbits)
Mutagenicity	Ames - negative Chromosome Aberration - negative
Repeated Dose Toxicity Feeding	 NOAEL 1 mg/kg/day rat NOAEL 20 mg/kg/day mouse

Inhalation Dermal (21 day)	NOAEL 190 mg/m^3 NOAEL 500 mg/kg/day rabbit
Reproductive Toxicity	~25 mg/kg/day
Developmental Toxicity	No data

*Robust summaries and References can be found in the IUCLID document.

Table 2. Test Plan for Isophthalonitrile

Endpoint	Data availability	Acceptable	Planned Testing
Physical-Chemical Data			
Molecular weight	✓	✓	No
Physical state	✓	✓	No
Melting Point	✓	✓	No
Boiling Point	✓	✓	No
Vapor Pressure	✓	✓	No
Partition Coefficient (logPow)	✓	✓	No
Water Solubility	✓	✓	No
Environmental Fate			
Photodegradation			
Fugacity (distribution)			
Biodegradability			
Water Stability			
Ecotoxicology			
Acute Fish Toxicity 96 hrs LC50	✓	✓	No
Acute Invertebrate Toxicity 48 hrs LC50	No	-	No
Algal Toxicity LC50	No	-	No
Mammalian Toxicology			
Acute Toxicity Oral Inhalation Dermal	 ✓ ✓ ✓	 ✓ ✓ ✓	No
Mutagenicity	✓	✓	No
Chromosome Aberration	✓	✓	No
Repeated Dose Toxicity	✓	✓	No
Reproductive Toxicity	✓	✓	No
Developmental Toxicity	No	-	No, based on

✓ Data available and considered adequate.